Physiological Regulation of E-Cadherin Adhesiveness

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Received date: March 06, 2018; Accepted date: April 06, 2018; Published date: April 10, 2018

Abstract

Physiological controls on cell adhesion mediated by E-cadherin have been frequently focused in the proliferation restraining. This can be given both by contact inhibition via the regulation of homotypic cadherin expression, by the control of adhesive strength, or even for the activation of proliferation mediated by growing factors. However, few studies have been conducted to evaluate the possible effects of hormones on the cell-cell adhesion mechanisms, during animal development and the maintenance of adult tissues and organs. Thus, the analysis of thyroid hormone influence on E-cadherin adhesive potential result highly challenging and promising field of research in cell biology.

Keywords: Cadherin; Thyroid hormones; Cell adhesion

Introduction

Growth factors are responsible for the crosstalk between cell proliferation, migration, and adhesion. As was early determined, the binding of the hepatocyte growth factor (HGF) to its receptor c-Met, causes cell-cell dissociation coupled to endocytosis of both E-cadherin and c-Met [1-3]. Fibroblastic growth factor (FGF) also induces E-cadherin endocytosis along with Fibroblastic growth factor receptor-1 (FGFR1), via a classical clathrin-mediated pathway [4]. In contrast, stimulation by Epidermal growth factor (EGF) causes Rac-1-dependent E-cadherin internalization by macropinocytosis, internalized-E-cadherin association with the sorting nexin 1 (SNX-1) preventing its degradation and facilitating the recycling back to the cell surface for AJs maintenance (Figure 1) [5]. Therefore, different growth factors-signaling pathways within the same cell can lead to very different fates for the E-cadherin internalization and surface-stabilization, possibly to achieve differentiated cell effects. Moreover, the co-regulation of E-cadherin and growth factor signaling is particularly prominent in various examples of Mesenchymal-Epithelial Transition (EMT) and tumorigenesis. Tumoral growth factor (TGFβ) signaling seems to be a key regulator for E-cadherin expression loss in response to Ras-Raf signaling during EMT [6-31]. E-cadherin mutants, in turn, reduce interactions between E-cadherin and EGFR, inducing EGFR dimerization, resulting in increased cell surface motility, enhanced activation of tumoral cells, and also E-cadherin internalization [3].

In contrast to growth factors-signaling on cell junctions, the hormonal physiological regulation of junctional communication has been scarcely analyzed. The most studies have evaluated hormonal regulation of gap junction-proteins expression, formation and/or maturation [13,15,32-50]. A long time ago we have focused on unraveling the functioning of E-cadherin mediated epithelial adhesion junctions during vertebrate development, and under hormonal influence [18,19,26-29]. Interesting, recently it was detected that the distribution/expression of N-, E- and VE-cadherins as well as α-catenin and F-actin were significantly altered in pancreatic islet cells of obese and diabetic mice [14]. In addition, it was found that the glucocorticoids promote respiratory epithelial barrier integrity by inducing protocadherin-1 expression [35].

Genomic and Non-Genomic Actions of Thyroid Hormones

It is widely recognized that thyroid hormones (TH) modulate energy metabolism, having a great influence on growth and development by independent mechanisms [51-61]. While thyroid calorigenesis is influenced predominantly via nuclear receptors that mediate synthesis of mitochondrial respiratory complexes and cell membrane sodium-potassium ATPase, it has been suggested that many of the TH effects over development are mediated via growth factors [16]. TH binding to thyroid hormone-nuclear receptors (TR), which
belong to the nuclear hormone receptor superfamily of transcription factors [39], stimulates growth hormone (GH) synthesis, and probably potentiates GH stimulation on somatomedin (SM) production as well, the erythropoietin (EP) production, being nerve growth factor (NGF) and epidermal growth factor (EGF), key players for erythrocyte production, autonomic and central nervous system maturation, and epidermal development, respectively [16].

The thyroid hormone receptor domain of integrin αvβ3 is at, or near the Arg-Gly-Asp (RGD) recognition site [2,9]. Another aspect to be considered is that T3 exerts its actions depending on the isoform of the receptor involved. Thus, TRα regulate the mitochondrial gene expression and metabolic function [61]. In addition, TRα or TRβ isoforms could act through the formation of a cytoplasmic complex with the PI3K-p85 subunit inducing the protein kinase Akt and nuclear translocation (Figure 2) [23]. THRA and THRB genes encode the TRα and TRβ isoforms respectively, which are ubiquitously expressed [62]. Moreover, depending on species, tissue or experimental systems, there are predominant TR cell isoforms, and each gene can generate different proteins using different promoters and/or alternative splicing [55,62].

Xenopus have two TRα genes and two TRβ genes due to tetraploid condition although when Xenopus laevis is a functional diploid organism, its genome shows several features reminiscent of its allotetraploid origin. Alternative splicing of the TRβ transcripts gives rise to two different isoforms for each TRβ gene [55]. In mammals, two genes encode for the T3 nuclear receptors TRα and TRβ [63]. Each gene generates different proteins using different promoters and/or alternative splicing [43,55,63]. The TRα locus codes for four isoforms, but only TRα1 can bind both T3 and DNA [1-63]. TRα1 and TRα2 result from the alternative splicing of a primary transcript [34]. TRα1 and TRα2 result from the alternative splicing of a secondary transcript, starting from an internal promoter that is located in the intron 7 [8]. TRα2, TRα1, and TRα2 behave as antagonists of TRα1 on its target genes through a mechanism that has not been characterized yet [8,34,48]. TRα1 and TRα2 have a widespread, ubiquitous expression, whereas the short TRα1 and TRα2 isoforms display restricted expression patterns [17]. The TRβ locus codes for four isoforms, including three receptors, TRβ1, TRβ2, and TRβ3, that result from three different transcription start sites [17,22]. The TRβ3 lacks the DNA-binding domain and behaves like a competitive inhibitor of the three TRβ and TRα1 receptors. Moreover, TRβ3 and TRα3 were only described in the rat genome [60]. TRβ1 displays a ubiquitous expression and is the main TR isoform expressed in the liver. TRβ2 expression is restricted to the pituitary gland, the hypothalamus-TRH neurons, the developing retina, and the inner ear. TRβ3 is expressed in liver, kidney and lung, whereas TRβ3 is present in skeletal muscles, heart, spleen, and brain [17,60]. Interestingly, almost all the TR isoforms are expressed in intestinal epithelial cells [47,48].

Usually, the T3-concentrations that lead to TRE-dependent responses occur in the picomolar range, whereas the minimum T3-concentrations, which activate Akt and eNOS, are somewhat higher, within the TR-dissociation constant value (i.e., 0.1-1 nM) [62]. It is unknown why higher concentrations of T3 are required for Akt and eNOS activation compared with that of TRE-dependent responses [23]. Through the isospecific differential TR-expression, TRα1 or TRβ1 mediate the activation of PI3-kinase/Akt/εNOS or PKB-mTOR-p70(S6K) pathways [7,23]. Additionally, due most of T3 is bound to carrier proteins such as thyroxine-binding globulin (TBG), albumin, and thyroid-binding pre-albumin in vivo, only 0.3% of T3, and 0.03% of T4 are unbound and free to interact with TR, and to produce biological activity [60]. In murine thyrocytes, TRβ1 is able to inhibit the Wnt/β-catenin pathway, through its interaction and consequent sequestration of β-catenin, resulting in cell proliferation down-modulation (Figure 3) [20].
At 24 h of T3 treatment while AJ number remain constant, Dm to IFABP behavior, a negative T3-responsive gene [53], the Rho small and desmosomes (Dm) led the major changes in epithelial remodeling. 

expression become more practically unchanged both at 24 h and day 5 of T3-treatment, as well (GEFs) and GTPase-activating protein (GAP) for each small GTPase respond directly to T3. Only Rac1-GAP12 showed a decrease of Rac1 and increase of Rap1.

significantly increased, suggesting the increase of epithelial adhesive plasticity, promoting cell proliferation and migration during gastrointestinal remodeling. At 5 days of T3-induction in agreement with a differentiated epithelium, the cell-cell distances of AJ and Dm return to those of mature epithelia, now of juvenile anurans. In contrast, a significant decrease of AJ and a significant increase of Dm were produced correlated with an impressive increase of apical complex junctions (ACJ), features of epithelial barrier strengthening (Figure 1). In addition, the morphometric IHC analysis has demonstrated that T3 exerts a positive regulatory effect on E-cadherin and β- and α-catenin expression and de novo synthesis in stomach epithelium during metamorphosis (Figure 2) [28].

From these results we can conclude that T3 mediates genomic response on E-cadherin, β-, α-catenin and Rac1 gastrointestinal genes, rapidly responding to adhesive plasticity and promoting lamellipodia formation, necessary during epithelial remodeling. In contrast, the master regulator of junctional E-cadherin stability, p120-catenin does not respond to T3, whereas Rap1 indirectly reacts to T3 during the reestablishment of mature epithelium. Rap1 is involved in the regulation of epithelial cell adhesion and migration. Rap1 is required for homotypic E-cadherin interactions [24]. Ligation of the extracellular domain of E-cadherin enhances Rap1activity, which in turn is necessary for the proper targeting of E-cadherin molecules to maturing cell-cell contacts [24]. In the presence of Rap1, afadin/nectin-partner and p120-catenin reduce endocytosis of E-cadherin that is not engaged in homophilic interactions and thereby further accumulates non-trans-interacting E-cadherin to the nectin-based cell-cell adhesion sites for the formation of AJ [25]. Rap1 contributes, in turn, to intestinal epithelial barrier stabilization in vivo [59]. Afadin is important for proper Rap1 activation and control of epithelial barrier function under basal and inflammatory conditions in vivo and in vitro. However, the exact mechanism by which Rap1 regulates these processes remains to be elucidated in future studies. Some studies suggest that active Rap1 stabilizes the barrier by dampening actomyosin contractility through the regulation of RhoA/ROCK-mediated actin dynamics [52].

Conclusion

Recently, we have proven that T3 is a key mediator of genomic response on E-cadherin, β-, α-catenin and Rac1 X. laevis gastrointestinal genes, which rapidly responding to adhesive plasticity, promoting lamellipodia formation, necessary during epithelial remodelling. Conversely, the master regulator of junctional E-cadherin stability, p120-catenin does not respond to T3, whereas Rap1 indirectly reacts to T3 during the re-establishment of mature epithelium. These behaviours open the possibility for alternative treatments to control proliferative disorders as colon cancer and other epithelial dysfunction diseases.

Acknowledgement

This study was supported by the grant CYT-UNER 6164–1 (to M. F. Izaguirre).

References


